ESC European Society of Cardiology

Europace (2025) **27**, euaf225
https://doi.org/10.1093/europace/euaf225

CLINICAL RESEARCH

Mapping and ablation outcomes of extra-pulmonary vein triggers in atrial fibrillation: single-centre retrospective study with consistent provocation protocol

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Received 7 June 2025; accepted after revision 9 September 2025; online publish-ahead-of-print 20 September 2025

Aims

Extra-pulmonary vein triggers (ExPVTs) are recognized as important contributors to atrial fibrillation (AF) recurrence after radio-frequency catheter ablation (RFCA). This study aimed to investigate the clinical characteristics, diagnostic value, and prognostic implications of isoproterenol-induced ExPVTs in patients undergoing *de novo* RFCA with circumferential pulmonary vein isolation (CPVI).

Methods and results

We analysed 2619 non-valvular AF patients (25.8% female, mean age 59.4 ± 10.9 years, 60.7% with paroxysmal AF) who underwent CPVI and standardized isoproterenol provocation testing; 98.2% also received empirical right atrial (RA) ablation. We evaluated the clinical and prognostic significance of ExPVTs for AF recurrence within 2 years, considering their anatomical location and targeted ablation status. ExPVTs were identified in 13.5% of patients. Lower mean left atrial (LA) voltage was independently associated with ExPVTs, irrespective of sex. Importantly, ExPVTs remained independently associated with AF recurrence [hazard ratio (HR) 1.81 (95% confidence interval 1.39–2.35)], alongside AF type, body mass index, LA volume index, and mean LA voltage as significant predictors. LA [HR 1.50 (1.04–2.17)] and septal [HR 1.51 (1.02–2.23)] triggers were significantly associated with recurrence, while RA triggers were not, given the high rate of empirical RA ablation (98.9%). Recurrence risk was highest in patients with multiple or unmappable triggers and in those without ExPVT-targeted ablation.

Conclusion

ExPVTs are strongly associated with lower LA voltage and carry independent prognostic value for AF recurrence, with outcomes varying by anatomical location and targeted ablation status. These findings underscore the importance of systematic ExPVT assessment and selective targeting in individualized ablation strategies.

Clinical Trial Registration

NCT02138695.

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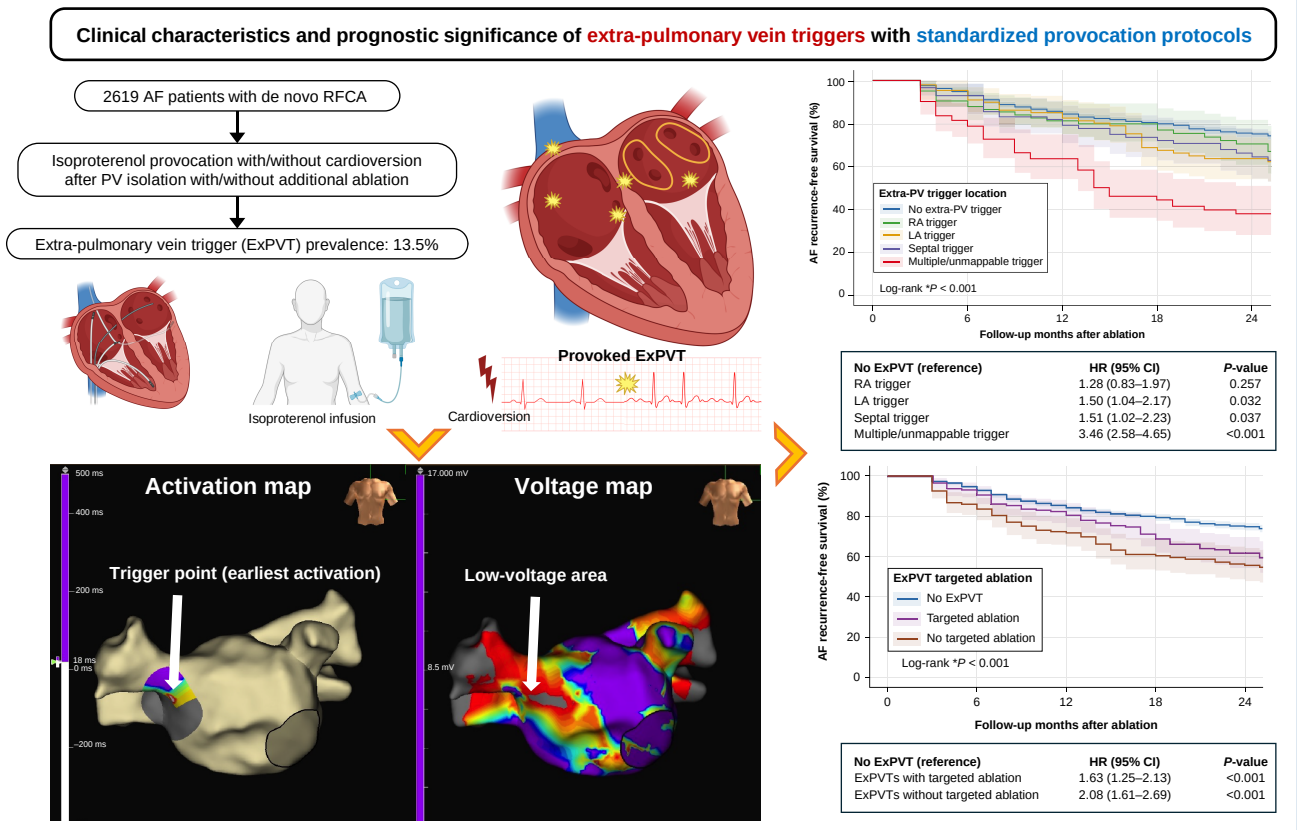
Graphical Abstract



Keywords Atrial fibrillation • Catheter ablation • Extrapulmonary vein triggers • Prognostic value

What's New?

- In this long-term, large-volume, single-centre study, we comprehensively analysed the clinical and prognostic significance of extra-pulmonary vein triggers (ExPVTs) after *de novo* ablation procedures with standardized provocation protocols and harmonized techniques.
- ExPVTs were associated with unfavourable baseline characteristics, including lower left atrial (LA) voltage irrespective of sex. Despite limited sensitivity, ExPVTs demonstrated high specificity and negative predictive value for predicting AF recurrence, supporting their diagnostic value.
- Prognostically, ExPVTs independently predicted AF recurrence, with the highest risk observed in multiple or unmappable triggers and in patients without targeted ablation. Location-specific effects were also evident, with LA and septal triggers conferring greater risk. These findings emphasize ExPVTs as enduring, clinically meaningful risk predictors that warrant systematic assessment and selective targeting in individualized ablation strategies.

Introduction

Pulmonary veins (PVs) are recognized as the primary source of ectopic beats that initiate atrial fibrillation (AF).[1] Since the late 1990s, when the critical role of PVs in AF initiation was first identified, circumferential pulmonary vein isolation (CPVI) has become an established catheter-based treatment strategy with consistent benefit in multiple randomized clinical trials.[2–5]

However, 10–20% of AF patients have ectopic beats originating from extra-PV areas, contributing significantly to AF recurrence after CPVI.[6–9] These extra-pulmonary vein triggers (ExPVTs) are defined as non-PV atrial ectopic beats triggering AF or focal atrial tachycardia (AT).[10] ExPVTs are known to play a crucial role in AF pathogenesis and are recognized as significant predictors of AF recurrence following CPVI.[6,7,11–13]

The prevalence of ExPVTs is reported to be higher in patients with persistent AF compared to those with paroxysmal AF, especially in individuals with specific risk factors such as advanced age, female sex, sleep apnoea, obesity, atrial structural remodelling, heart failure, cardiomyopathy, or valvular heart disease.[14,15] ExPVTs are often challenging to identify and eliminate, and recent studies have reported that AF originating from these sources is associated with worse outcomes compared to AF originating from PVs.[8] Although no randomized prospective trials have specifically evaluated whether ablating ExPVTs improves clinical outcomes, several observational studies suggest that ExPVTs are clinically relevant and appropriate targets for ablation.[7,11,12] Current expert consensus statements recommend ablation of reproducible focal trigger outside the PV ostia initiating AF following CPVI to reduce AF recurrence.[16] As a result, there is growing interest in evaluating the potential of catheter-based techniques to target these focal triggers.[10]

Despite the clinical impact of ExPVT on AF recurrence, evidence regarding their clinical significance and prognostic importance in *de novo* radiofrequency catheter ablation (RFCA) remains limited. Although ablation of ExPVTs has been previously reported, randomized trials in this

field remain extremely challenging due to the lack of standardized protocols across centres. Moreover, clarifying the specific characteristics of ExPVTs and their association with clinical outcomes is crucial for optimizing treatment strategies and improving prognosis in patients undergoing RFCA.

In this study, we comprehensively analysed the clinical characteristics, diagnostic relevance, and prognostic implications of ExPVTs following CPVI for AF recurrence after *de novo* ablation procedures, using long-term, large-volume, single-centre data with consistent provocation and harmonized ablation techniques. Through this approach, we aimed to provide robust and pragmatic insights into the role of ExPVTs in real-world clinical practice.

Methods

Study population and design

The study was performed as a single-centre retrospective cohort study. The protocol adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board at Yonsei University Health System. All patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort (ClinicalTrials.gov identifier: NCT02138695). A total of 5572 patients diagnosed with AF who underwent RFCA from March 2009 to December 2023 were screened. After excluding patients with prior AF ablations, concomitant AF surgery, significant valvular disease or surgery, missing post-procedural isoproterenol tests, or lack of follow-up data, we included 2619 AF patients who underwent consistent post-procedural isoproterenol provocation tests after CPVI. The decision to perform isoproterenol provocation testing was primarily determined at the discretion of the operating electrophysiologist.

These patients were categorized based on the presence or absence of ExPVTs, and further sub-categorized by the approximate location of these triggers—single right atrial (RA)-sided, left atrial (LA)-sided, septal, or multiple/unmappable—for subsequent analysis. (*Figure 1*). Before ablation, the absence of LA thrombi was confirmed by transoesophageal echocardiography, intracardiac echocardiography, or computed tomography (CT). All antiarrhythmic drugs (AADs) were discontinued for at least five half-lives, with amiodarone stopped at least 4 weeks before the procedure.

Echocardiographic parameters and other parameters

All patients included in the study underwent transthoracic echocardiography (Sonos 5500, Philips Medical Systems, Andover, MA, USA or Vivid 7, GE Vingmed Ultrasound, Horten, Norway) before RFCA and again 1-year post-procedure. Measurements of cardiac chamber size, left ventricular ejection fraction (LVEF), *trans*-mitral Doppler flow velocity, and the E/E_m ratio (early diastolic mitral inflow velocity to early diastolic mitral annular velocity) were acquired according to the guidelines of the American Society of Echocardiography. The anatomical structures of the LA and PVs were assessed using three-dimensional (3D) CT (64-channel, Light Speed Volume CT; Brilliance 63, Philips, Best, The Netherlands) within a week before RFCA. LA volume and mean LA wall thickness were quantified from ECG-gated CT images using validated software (ITK-SNAP and AMBER), as described in previous studies.[17] Automated quantification of epicardial adipose tissue (EAT) was performed on the same images using a previously validated segmentation framework based on multi-task convolutional neural networks.[18] The model was trained on a manually annotated cardiac CT dataset and evaluated for consistency with expert manual segmentations. Briefly, the pericardial boundary was identified by the artificial intelligence model and EAT was extracted by applying a Hounsfield unit threshold range of −190 to −30 HU.

Electro-anatomical mapping and catheter ablation

Intracardiac electrograms were recorded using the Prucka CardioLab™ Electrophysiology system (General Electric Medical Systems, Inc., Milwaukee, WI, USA), and 3D electro-anatomical maps were created with the NavX (Abbott, Inc., Chicago, IL, USA) or CARTO (Biosense Webster, Diamond Bar, CA, USA) systems, using a PV-mapping catheter (Reflexion Spiral, Advisor™ FL Circular, or HD Grid from Abbott, Inc.; AFocus, Lasso, PentaRay, or OctaRay from Biosense Webster, Inc.) through a long sheath. The 3D geometries of the LA and PVs were constructed using the 3D mapping system and subsequently merged with 3D spiral CT images. Transseptal punctures were performed based on operator discretion (single or double punctures). After the puncture, systemic anticoagulation was initiated with an intravenous bolus of heparin (200 IU/kg) and maintained with intermittent boluses to keep the activated clotting time between 350 and 400 s. Pulmonary venograms were obtained to precisely align the 3D map with CT and fluoroscopy, except in patients with significant renal impairment.

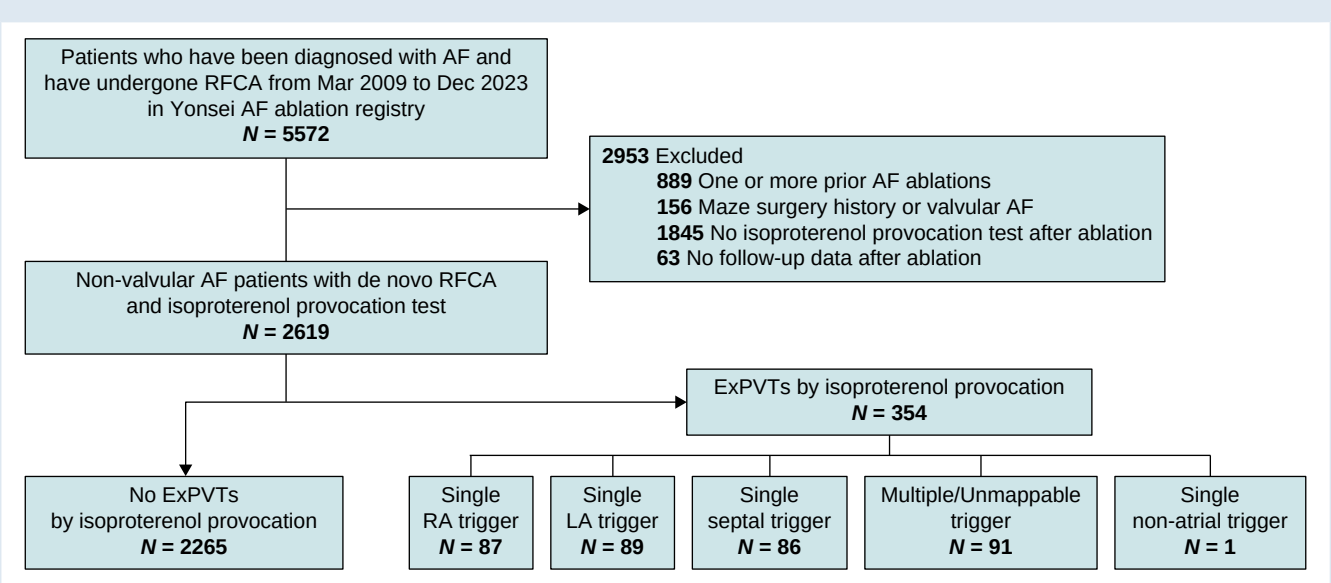


Figure 1 Flow chart and sample selection of this study. Abbreviations: AF, atrial fibrillation; ExPVT, extra-pulmonary vein trigger; LA, left atrium; RA, right atrium; RFCA, radio-frequency catheter ablation.

RFCA was performed using an open-irrigated tip catheter (Celsius, NaviStar ThermoCool, ThermoCool SF, or ThermoCool SmartTouch from Biosense Webster Inc.; Coolflex, FlexAbility, or TactiCath from Abbott Inc.), with radiofrequency power ranging from 25 to 60 W, across the long study period. The ablation endpoint at each site was defined as either a >10% drop in impedance from baseline or an >80% reduction in local electrogram voltage amplitude. Complete CPVI with a bidirectional block was achieved in all patients. Empirical linear ablation, including cavotricuspid isthmus (CTI) block, superior vena cava (SVC)-septal line, roofline, posterior–inferior line (posterior box lesion), anterior line, left lateral isthmus ablation, or complex fractionated electrogram ablation, was performed at the operator's discretion.

Isoproterenol provocation test and procedure endpoint

Following the protocol-based ablation, AF or AT was induced using 10-s high-current burst pacing (10 mA, pulse width 5 ms, Bloom Associates, Denver, CO, USA) from the high RA electrodes, starting with a pacing cycle length of 250 ms and gradually decreasing to 120 ms. Isoproterenol (5–20 μg/min, adjusted based on β-blocker use, aiming for heart rate of 120 bpm) was infused for a minimum of 3 min before induction and continued for 3 min after AF or AT was induced. In cases of sustained AF or AT, internal cardioversion was performed using biphasic shocks (2–20 J) synchronized to the R wave (Lifepak12, Physiocontrol Ltd, Redmond, WA, USA). All procedures were conducted under conscious sedation, with deep sedation induced prior to electrical cardioversion. The procedure was considered complete when there was no immediate recurrence of AF within 10 min following isoproterenol infusion, with or without cardioversion.

If AF triggers were identified under the effect of isoproterenol, potential ExPVT locations were determined using available pre-positioned multielectrode diagnostic catheters and PV mapping catheters to identify the earliest activation point. Operators then reported the potential ExPVT origin sites by anatomical location following a standardized institutional workflow (*Figure 2*). Based on the bipolar electrograms and activation mapping, ExPVT foci were ablated with 35–50 W for 10 s per lesion until eliminated. ExPVTs were defined as non-PV ectopic trigger foci that initiated AF or other sustained atrial arrhythmias lasting ≥30 s (e.g. regular AT/organized flutter), identified via isoproterenol provocation after confirmed bidirectional PV block. Isolated premature atrial contractions (PAC) that did not induce AF or sustained AT were not considered ExPVTs and were not ablation targets. Reproducibility was assessed within the same provocation sequence. Repeat isoproterenol provocation after targeted ablation was not routinely performed because of the need for repeated cardioversion and considerable patient discomfort, though it was considered when a focus was highly reproducible.

Post-ablation management and follow-up

Patients were discharged without AADs, except for those who experienced recurrent ExPVTs following the RFCA procedure, symptomatic

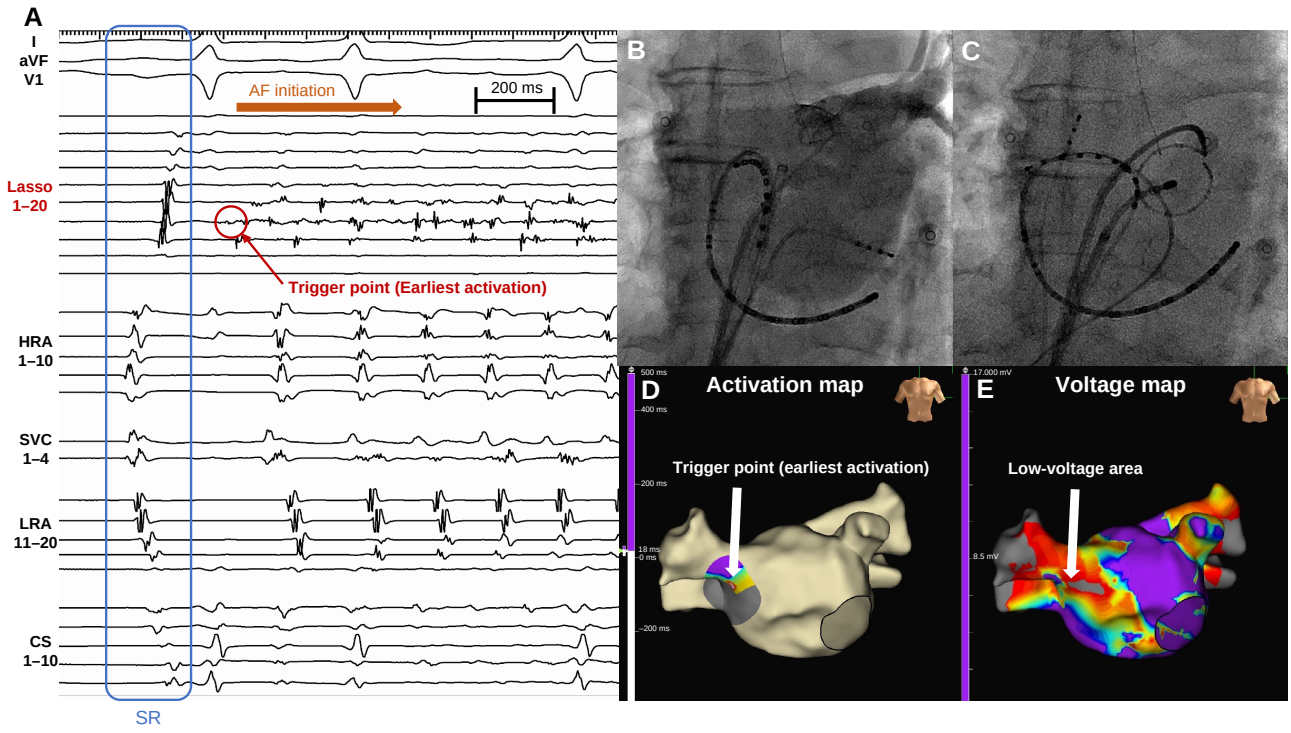


Figure 2 Representative example of an induced ExPVT from the LA septum during isoproterenol provocation test. (*A*) Intracardiac electrograms showing AF initiation by an ExPVT induced during provocation. The earliest activation (circle marked by a pointed arrow) is recorded by the circular mapping catheter positioned at the LA septum, consistent with panels *D* and *E*. (*B*) Fluoroscopic image (AP view) showing a left atriogram with pulmonary venogram and initial positioning of multielectrode diagnostic catheters. (*C*) Standardized catheter configuration (AP view) during provocation testing, including a quadripolar catheter in the SVC, a decapolar across the high RA and septum, and a duodecapolar along the CS and low RA. A PV mapping catheter, typically positioned at the LA posterior wall, varied in type depending on availability, operator preference, and patient characteristics. (*D*) Electroanatomical activation map identifying the earliest trigger point (white arrow) of the ExPVT from the LA septum. (*E*) Electroanatomical voltage map showing a low-voltage area at the LA septum compatible with the AF trigger site. Abbreviations: AF, atrial fibrillation; AP, anterior posterior; CS, coronary sinus; ExPVT, extra-pulmonary vein trigger; HRA, high right atrium; LA, left atrium; LRA, low right atrium; PV, pulmonary vein; RA, right atrium; SR, sinus rhythm; SVC, superior vena cava.

frequent atrial premature beats (APBs), non-sustained AT, or early AF recurrence as detected by telemetry during hospitalization. Follow-up visits were scheduled regularly at 1, 3, 6, and 12 months, then every 6 months, or as needed if symptoms occurred. At each visit, patients underwent an ECG, with 24-h Holter monitoring at 3 and 6 months, every 6 months for the first 2 years, annually between 2 and 5 years, and biannually thereafter. Event monitor recordings were also obtained if patients reported palpitations suggestive of arrhythmia recurrence. Atrial fibrillation recurrence was defined as any AF or AT episode lasting at least 30 s. Early recurrence was classified as any AF episode documented within the 3-month blanking period, while clinical recurrence was defined as any AF episode documented more than 3 months after the procedure.

The primary outcome was AF recurrence within 2 years following RFCA. This timeframe was chosen to minimize the impact of long-term atrial remodelling due to cardiac ageing on AF recurrence, and to specifically examine the influence of ExPVT on mid-term recurrence after CPVI, while accounting for AF recurrence potentially influenced by technical factors related to RFCA.

Holter monitor recordings and heart rate variability analysis

Heart rate variability (HRV) was analysed using a GE Marquette MARS 8000 Holter analyser (General Electric Medical Systems, Chicago, IL, USA) based on 24-h Holter monitor recordings. Premature ventricular complexes (PVC), PACs, electrical artefacts, low-quality recordings, and noise were excluded from the analysis.

The time-domain HRV parameters analysed included mean heart rate, mean RR interval (mean NN interval), and the root mean square of differences between successive NN intervals (rMSSD). The rMSSD serves as an indicator of beat-to-beat variance in heart rate, with higher rMSSD and lower mean heart rate reflecting increased HRV.[19] The frequency-domain HRV parameters included very-low-frequency components (<0.04 Hz), low-frequency components (LF; 0.04–0.15 Hz), high-frequency components (HF; 0.15–0.4 Hz), and the LF/HF ratio. HF and rMSSD represent parasympathetic nervous activity, while LF reflects both sympathetic and parasympathetic contributions. The LF/HF ratio is an index of sympatho-vagal balance.[20] All Holter recordings were analysed using the automated rhythm classification algorithm embedded in the GE Marquette MARS 8000 system, which detects and quantifies non-sinus beats, including PACs and PVCs. Only segments with >90% sinus beats were included for HRV analysis, based on the algorithm's classification. Ambiguous or artefact-labelled segments were reviewed and confirmed to ensure data quality.

Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD) and compared using an independent two-sample *t*-test or Mann–Whitney *U*-test. Categorical variables were expressed as numbers with percentages and compared using either Pearson's chi-squared test or Fisher's exact test. Univariable and multivariable logistic regressions were applied to identify predictive variables associated with the presence of ExPVTs. Two-by-two tables with accuracy metrics were used to evaluate the diagnostic accuracy of ExPVTs for detecting AF recurrence within 2 years, with 95% confidence intervals (CIs) estimated using the Wilson score interval. Kaplan–Meier analysis with the log-rank test was employed to calculate AF recurrence-free survival after RFCA and to compare recurrence rates according to the location, number, and targeted ablation of ExPVTs. Event rates were presented as events per 100 person-year (PY) with 95% CIs. Multivariable Cox regression was performed to evaluate the independent predictive value of ExPVTs for AF recurrence, alongside other clinical predictors. In addition, hazard ratios (HRs) were estimated according to the location and targeted ablation of ExPVTs, adjusting for baseline clinical risk factors. The analysis also aimed to identify predictors of no clinical AF recurrence within 2 years after RFCA in patients with ExPVTs. Age, sex, and variables with statistical significance in the univariable analysis were included in the multivariable model. Since mean LA voltage was not available for all subjects, two levels of adjustment were applied: Model 1 excluded mean LA voltage, and Model 2 included it.

A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using R version 4.2.3 software (The R Foundation, www.R-project.org, Vienna, Austria).

Results

Baseline characteristics and predictive variables for the presence of extra-pulmonary vein triggers

Table 1 summarizes the baseline clinical, imaging, and procedural characteristics according to the presence of ExPVTs. The ExPVTs were identified in 13.5% of patients undergoing *de novo* RFCA. These patients were older, had a higher proportion of females and non-paroxysmal AF, longer diagnosis-to-ablation time (DAT), lower body mass index (BMI), and higher CHA2DS2-VASc scores. Echocardiography revealed higher LVEF and larger LA volume indices, with CT imaging showing larger LA volumes. Atrial EAT volumes were smaller, and mean LA voltage was lower in patients with ExPVTs. They also showed higher rates of early recurrence within 3 months and clinical recurrence within 2 years post-procedure. When baseline characteristics were compared across ExPVT locations (see Supplementary material online, *Table S1*), patients with multiple or unmappable triggers were more likely to have non-paroxysmal AF, smaller atrial EAT volumes, and significantly lower mean LA voltage compared with those with single triggers. These features suggest more advanced atrial remodelling, accompanied by higher rates of both early and clinical recurrence. Details of procedural complications are presented in Supplementary material online, *Table S2*.

In the multivariable logistic regression analysis (see Supplementary material online, *Table S3*), mean LA voltage [odds ratio (OR) 0.32 (95% CI 0.20–0.51)] was independently associated with the presence of ExPVTs, irrespective of sex, with similar effect sizes in men [OR 0.54 (95% CI 0.37–0.77)] and women [OR 0.61 (95% CI 0.37–0.99)]. In male patients, longer DAT remained a significant predictor, while in female patients, larger LA volume and lower left ventricle end-diastolic dimension (LVEDD) were independently associated with ExPVTs. A history of transient ischaemic attack (TIA) was also significantly associated with ExPVTs in women [OR 3.64 (95% CI 1.55–8.53)] (*Figure 3*).

Diagnostic accuracy and prognostic value of extra-pulmonary vein triggers for atrial fibrillation recurrence

The diagnostic accuracy of ExPVTs for predicting AF recurrence within 2 years after RFCA was assessed (see Supplementary material online, *Figures S1*). The prevalence of ExPVTs was 24.1%. The sensitivity of ExPVTs for predicting AF recurrence was 20.3% (95% CI 17.5–23.4%), while the specificity was 88.7% (95% CI 87.1–90.2%). The positive predictive value (PPV) was 36.2% (95% CI 31.3–41.4%), whereas the negative predictive value (NPV) was 77.8% (95% CI 75.8–79.7%). When stratified by sex, men exhibited a slightly lower prevalence of ExPVTs, along with higher specificity and higher NPV compared to women.

After excluding patients who underwent targeted ablation for ExPVTs, the diagnostic accuracy of ExPVTs was reassessed, showing an increase in specificity from 88.7% to 94.5%, while NPV remained unchanged. In contrast, when patients who were prescribed AADs after RFCA were excluded, the specificity increased from 88.7 to 92.2%, and notably, the NPV increased substantially from 77.8 to 86.6% (see Supplementary material online, *Figures S2* and *S3*).

Importantly, in multivariable Cox regression analyses assessing the prognostic value of ExPVTs for AF recurrence beyond established clinical predictors, the presence of ExPVTs remained independently and strongly associated with AF recurrence [HR 1.81 (95% CI 1.39–2.35)], alongside with AF type, BMI, LA volume index, and mean LA voltage as independent predictors (see Supplementary material online, *Table S4*).

Table 1 Baseline clinical, imaging, and procedural characteristics according to the presence of ExPVTs

	Overall N = 2619	Absence of ExPVTs N = 2265	Presence of ExPVTs N = 354	P-value
Age, years	59.4 ± 10.9	59.1 ± 10.9	61.2 ± 10.5	0.001
Female, *n* (%)	675 (25.8%)	548 (24.2%)	127 (35.9%)	<0.001
Paroxysmal AF, *n* (%)	1589 (60.7%)	1393 (61.5%)	196 (55.5%)	0.037
Diagnosis to ablation time, months	38.2 ± 43.4	36.4 ± 41.5	48.0 ± 51.1	0.001
BMI, kg/m^2	24.9 ± 3.0	25.0 ± 3.0	24.6 ± 3.0	0.016
CHA2DS2-VASc	1.8 ± 1.5	1.8 ± 1.5	2.0 ± 1.6	0.026
Comorbidities, *n* (%)				
Hypertension	1187 (45.3%)	1019 (45.0%)	168 (47.5%)	0.418
Diabetes mellitus	417 (15.9%)	372 (16.4%)	45 (12.7%)	0.090
Stroke	292 (11.1%)	255 (11.3%)	37 (10.5%)	0.721
Transient ischaemic attack	33 (1.3%)	25 (1.1%)	8 (2.3%)	0.119
Heart failure	404 (15.4%)	347 (15.3%)	57 (16.1%)	0.765
Vascular disease	256 (9.8%)	227 (10.0%)	29 (8.2%)	0.326
Echocardiographic parameters				
LA dimension, mm	41.5 ± 6.3	41.5 ± 6.3	41.6 ± 6.5	0.739
LA volume index, mL/m^2	38.2 13.3	37.8 ± 13.2	40.9 ± 13.2	<0.001
LV ejection fraction, %	63.0 ± 8.5	62.8 ± 8.6	63.8 ± 7.5	0.025
LVEDD, mm	50.3 ± 13.6	50.4 ± 14.6	49.6 ± 4.0	0.017
E/E_m	10.2 ± 4.0	10.1 ± 4.0	10.5 ± 4.0	0.153
Other parameters				
LA volume by CT, ml	153.6 ± 45.9	152.3 ± 45.7	162.0 ± 45.9	<0.001
Mean LA wall thickness by CT, mm	1.8 ± 0.4	1.8 ± 0.4	1.8 ± 0.4	0.072
EAT by CT (atrium), cm^3	66.8 ± 34.3	67.7 ± 34.2	60.9 ± 34.4	0.008
EAT by CT (ventricle), cm^3	43.3 ± 23.7	43.7 ± 23.9	40.5 ± 22.2	0.072
Mean LA pressure (NSR), mmHg	11.9 ± 7.0	11.8 ± 7.2	12.0 ± 6.0	0.755
Mean LA pressure (AF), mmHg	13.0 ± 6.6	13.1 ± 6.2	12.8 ± 8.7	0.686
Mean LA voltage, mV (*n* = 2090)	1.4 ± 0.6	1.4 ± 0.6	1.2 ± 0.5	<0.001
Ablation strategy, *n* (%)				
CPVI	2619 (100.0%)	2265 (100.0%)	354 (100.0%)	1.000
CTI block	2547 (97.3%)	2202 (97.2%)	345 (97.5%)	0.935
SVC–septal line	2100 (80.2%)	1786 (78.9%)	314 (88.7%)	<0.001
Posterior box isolation	649 (24.8%)	557 (24.6%)	92 (26.0%)	0.617
Anterior linear line	536 (20.5%)	419 (18.5%)	117 (33.1%)	<0.001
Procedural parameters				
Procedure time (min)	165.5 ± 58.3	164.6 ± 58.9	171.3 ± 54.4	0.056
Ablation time (s)	4076.2 ± 1875.3	4090.0 ± 1874.8	3988.0 ± 1878.9	0.342
Complications[a], *n* (%)	92 (3.5%)	73 (3.2%)	19 (5.4%)	0.060
Major complications[a], *n* (%)	50 (1.9%)	41 (1.8%)	9 (2.5%)	0.467
Follow-up duration (months)	18.1 ± 7.8	18.4 ± 7.7	16.3 ± 8.1	<0.001
Early recurrence within 3 months after RFCA, n (%)	769 (29.4%)	611 (27.0%)	158 (44.6%)	<0.001
Clinical recurrence within 2 years after RFCA, *n* (%)	631 (24.1%)	503 (22.2%)	128 (36.2%)	<0.001

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as number (percentage).

[a]Complications resulting in permanent injury or death, requiring intervention, or necessitating hospitalization for more than 48 h include sinus node dysfunction, sick sinus syndrome, pulmonary vein stenosis, pericarditis, and major complications such as cardiac tamponade, haematemesis, arteriovenous fistula, and phrenic nerve palsy.

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CPVI, circumferential pulmonary vein isolation; CT, computed tomography; CTI, cavo-tricuspid isthmus; EAT, epicardial adipose tissue; E/E_m, mitral inflow velocity/mitral annulus tissue velocity; ExPVT, extra-pulmonary vein trigger; LA, left atrium; LV, left ventricle; LVEDD, left ventricle end-diastolic dimension; N, numbers; NSR, normal sinus rhythm; RFCA, radio-frequency catheter ablation; SVC, superior vena cava.

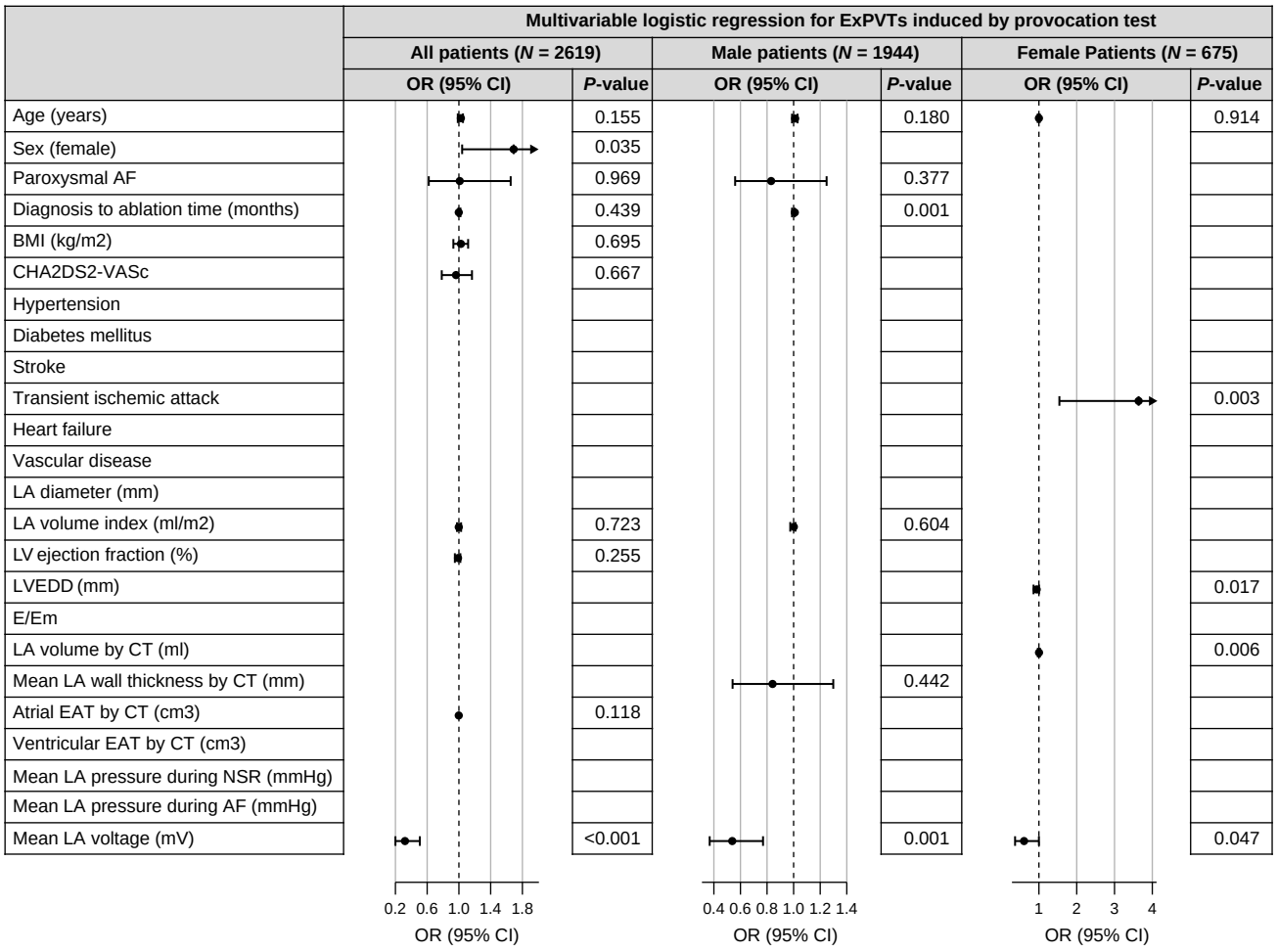


Figure 3 Multivariable logistic regression analysis for identifying predictive variables of ExPVTs stratified by sex. Variables used in multivariable analyses: age, sex, and variables with statistical significance in the univariable analysis were included in the multivariable analysis. In sex-stratified analyses, sex was excluded from the models by design. Abbreviations: AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; CT, computed tomography; EAT, epicardial adipose tissue; E/Em, mitral inflow velocity/mitral annulus tissue velocity; ExPVT, extra-pulmonary vein trigger; LA, left atrium; LV, left ventricle; LVEDD, left ventricle end-diastolic dimension; N, numbers; NSR, normal sinus rhythm; OR, odds ratio.

Anatomical locations of extra-pulmonary vein triggers, targeted ablation, and the risk of atrial fibrillation recurrence

Potential anatomical origins of ExPVTs are detailed in Supplementary material online, *Table S5*, with the septum, followed by the coronary sinus and SVC, representing the most common origins. The risk of AF recurrence within 2 years after RFCA was analysed according to the location of ExPVTs and whether targeted ablation was performed (*Table 2*). In patients without ExPVTs, the AF recurrence rate was 14.46 per 100PY and served as the reference. Those with a single RA trigger showed a non-significant increase [18.12 per 100PY; HR 1.28 (95% CI 0.83–1.97)], while single LA and septal triggers were significantly associated with higher recurrence (22.10 and 21.77 per 100PY; HRs 1.50 and 1.51, respectively). The highest risk was observed in patients with multiple or unmappable triggers[49.75 per 100PY; HR 3.46 (95% CI 2.58–4.65)]. Targeted ablation for ExPVTs was associated with lower recurrence (23.30 per 100PY; HR 1.63) compared to no ablation (30.48 per 100PY; HR 2.08), though outcomes remained inferior to those without ExPVTs. Kaplan–Meier analyses (*Figures 4* and *5*) confirmed these trends. Consequently, high-risk ExPVT patterns, such as multiple or unmappable triggers and absence of targeted ablation, had the poorest rhythm outcomes overall. The 5-year subgroup analysis confirmed that these high-risk patterns consistently conferred excess risk across all eras, whereas outcomes after ExPVT-targeted ablation in the latest era improved to the point that recurrence risk was no longer significantly higher than in patients without ExPVTs, reflecting the beneficial impact of technological advances while preserving the fundamental prognostic relevance of ExPVTs (see Supplementary material online, *Table S6*).

Supplementary material online, *Table S7* shows that patients who underwent ExPVT-targeted ablation were generally younger, more often female, and exhibited overall less advanced atrial remodelling compared to those who did not. Atrial fibrillation recurrence remained highest in patients with multiple or unmappable triggers, regardless of targeted ablation, whereas no significant difference was observed in those with single triggers vs. no ExPVTs. Among patients with multiple or unmappable triggers, targeted ablation tended to reduce recurrence, though the difference was not statistically significant (see Supplementary material online,

Table 2 Events and risk analysis of AF recurrence within 2 years after RFCA according to the location of ExPVTs and the targeted ablation for ExPVTs

	Number of events/ total number	Event rates per 100PY (95% CI[a])	Adjusted HR[b] (95% CI)	*P*-value
Location of ExPVT				
No ExPVT	503/2265	14.46 (13.22–15.72)	1.00 [Reference]	- [Reference]
RA trigger	22/87	18.12 (10.71–26.36)	1.28 (0.83–1.97)	0.257
LA trigger	30/89	22.10 (14.73–30.20)	1.50 (1.04–2.17)	0.032
Septal trigger	27/86	21.77 (13.71–30.65)	1.51 (1.02–2.23)	0.037
Multiple/unmappable trigger	49/91	49.75 (36.55–63.96)	3.46 (2.58–4.65)	<0.001
Targeted ablation for ExPVT				
No ExPVT	503/2265	14.46 (13.22–15.72)	1.00 [Reference]	- [Reference]
ExPVTs with targeted ablation	61/184	23.30 (17.57–29.41)	1.63 (1.25–2.13)	<0.001
ExPVTs without targeted ablation	67/170	30.48 (23.20–37.76)	2.08 (1.61–2.69)	<0.001

[a]The 95% CIs for event rates was estimated using a Poisson distribution.
[b]Adjusted for baseline clinical risk factors that showed significant differences depending on the presence of ExPVTs.
Abbreviations: AF, atrial fibrillation; CI, confidence interval; ExPVT, extra-pulmonary vein trigger; HR, hazard ratio; LA, left atrium; PY, person-year; RA, right atrium.

Tables S8 and *S9*, Supplementary material online, *Figures S4A* and *S4B*). Post hoc analyses stratified by AAD use after RFCA showed that recurrence was more frequent in patients prescribed AADs, particularly among those with multiple or unmappable triggers (see Supplementary material online, *Table S10*, Supplementary material online, *Figures S4C* and *S4D*).

Changes in heart rate variability parameters according to ExPVT-targeted ablation

Pre-RFCA HRV parameters did not significantly differ based on the presence of ExPVTs or whether targeted ablation was performed (see Supplementary material online, *Table S11*). However, post-RFCA HRV parameters, except for the LF/HF ratio, showed significant differences that persisted for up to 1 year of follow-up. Specifically, patients with ExPVTs exhibited a lower mean heart rate and higher rMSSD, LF, and HF compared to those without ExPVTs, with these differences being more pronounced in ExPVT patients who did not undergo targeted ablation. Consistent findings were observed in the mean trend analysis of HRV parameters pre- and post-ablation according to the presence and targeted ablation of ExPVTs (see Supplementary material online, *Figure S5*).

Clinical characteristics and predictive variables associated with atrial fibrillation recurrence in patients with extra-pulmonary vein triggers

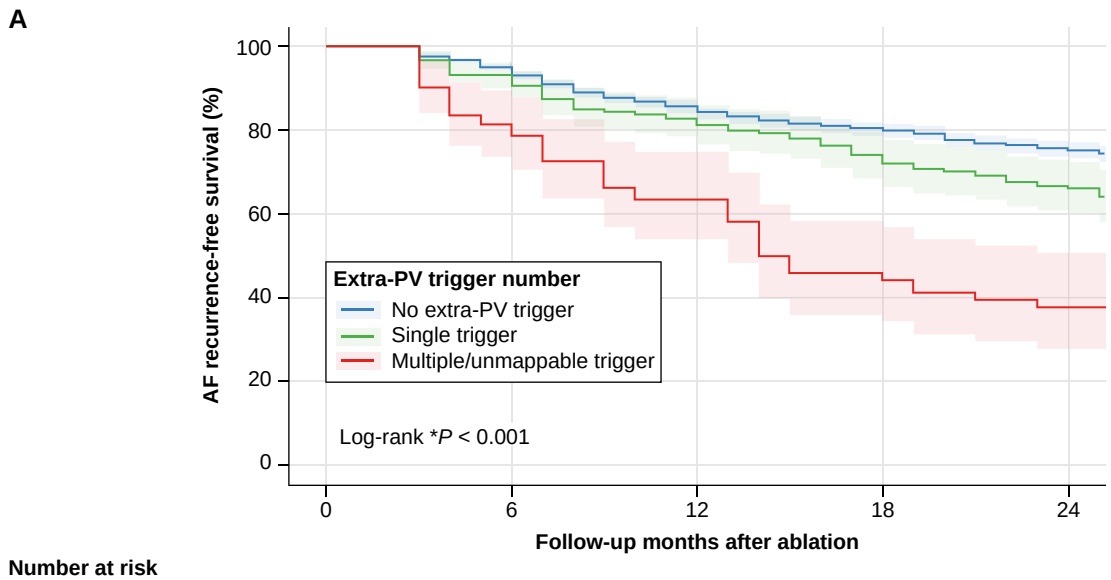
Supplementary material online, *Table S12* compares the clinical and procedural characteristics of patients with ExPVTs who did not experience AF recurrence within 2 years to those who experienced recurrence. Patients with ExPVTs but no recurrence predominantly had paroxysmal AF and exhibited less atrial remodelling characterized by smaller LA and LV sizes and volumes, higher LVEF, and higher mean LA voltage. Notably, patients with ExPVTs but no recurrence underwent fewer additional empirical ablations, such as CTI block, posterior box isolation, and anterior linear line, other than CPVI.

In the Cox regression analysis, significant predictors of no AF recurrence within 2 years in ExPVT patients were higher LVEF and lower mean LA wall thickness. Importantly, mean LA wall thickness was independently associated with no AF recurrence in ExPVT patients in the multivariable analysis (see Supplementary material online, *Table S13*). After excluding patients with targeted ablation for ExPVTs or those prescribed AADs following RFCA, the multivariable analysis identified no significant predictors of AF recurrence-free status in ExPVT patients (see Supplementary material online, *Tables S14* and *S15*).

Discussion

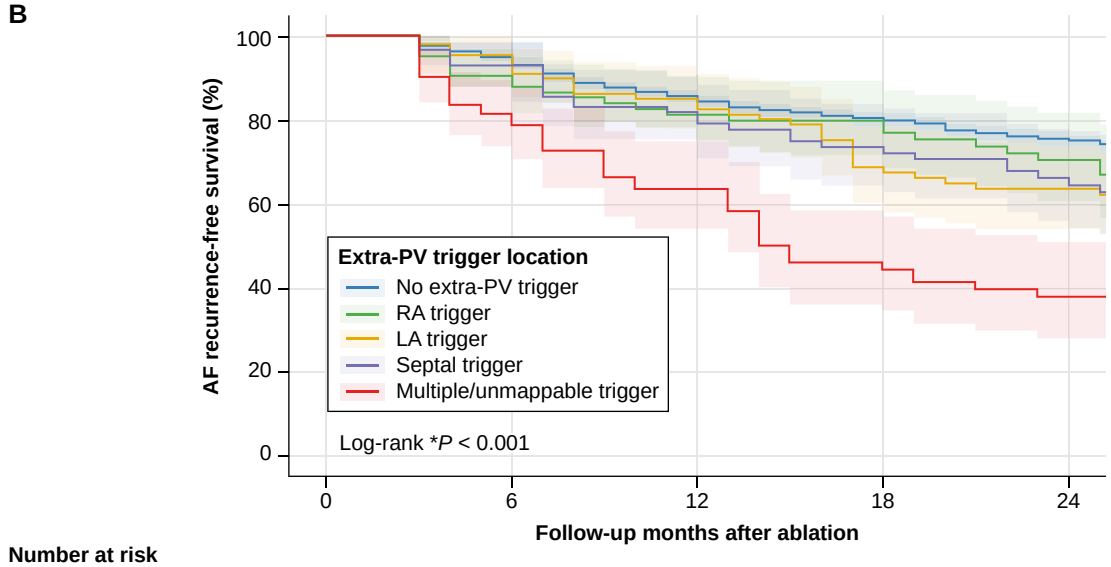
Main findings

In this single-centre, retrospective cohort study, we comprehensively analysed the clinical characteristics and highlighted key findings regarding the prognostic value of isoproterenol-induced ExPVTs after CPVI in *de novo* AF ablation procedures. ExPVTs were associated with unfavourable baseline characteristics. Notably, lower mean LA voltage was independently and consistently associated with the presence of ExPVTs, irrespective of sex, whereas additional sex-specific predictors differed, including longer DAT in men, and larger LA volume, lower LVEDD, and a history of TIA in women. Despite limited sensitivity and PPV, ExPVTs demonstrated high specificity and NPV for predicting AF recurrence within 2 years post-ablation, indicating that the absence of ExPVTs may be more reliably used to predict non-recurrence of AF in the mid-term after RFCA. Importantly, beyond this diagnostic value, ExPVTs also carried independent prognostic value for AF recurrence, supporting their role as a clinically meaningful risk factor beyond established predictors. Our findings also complement our prior study identifying non-PV triggers as a key contributor to very late AF recurrence beyond 5 years post-ablation.[21] The consistent link between ExPVTs and recurrence underscores their lasting clinical relevance across both mid- and long-term follow-up, supporting systematic ExPVT assessment even at the *de novo* ablation stage. Additionally, AF recurrence risk varied by ExPVT locations, with LA and septal triggers showing higher recurrence and RA triggers showing no significant association. Multiple or unmappable triggers were consistently linked to the worst outcomes regardless of targeted ablation. The presence of ExPVTs and targeted ablation significantly influenced post-RFCA HRV parameters, with these differences more noticeable when targeted ablation was not performed.



Number at risk

No extra-PV trigger	2265	2024	1734	1512	1283
Single trigger	263	232	189	158	131
Multiple/unmappable trigger	91	68	49	31	21



Number at risk

No extra-PV trigger	2265	2024	1734	1512	1283
RA trigger	87	71	59	52	41
LA trigger	89	84	69	53	48
Septal trigger	86	76	60	52	41
Multiple/unmappable trigger	91	68	49	31	21

Figure 4 Kaplan–Meier survival curves for AF recurrence-free survival after RFCA (*A*) according to the presence and number of ExPVTs and (*B*) according to the location of ExPVTs. The incidence curves and corresponding *P*-values for comparing the ExPVT groups were derived from the Kaplan–Meier method with the log-rank test. The shaded area represents 95% CIs. Abbreviations: AF, atrial fibrillation; CI, confidence interval; ExPVT, extra-pulmonary vein trigger; LA, left atrium; RA, right atrium; RFCA, radio-frequency catheter ablation.

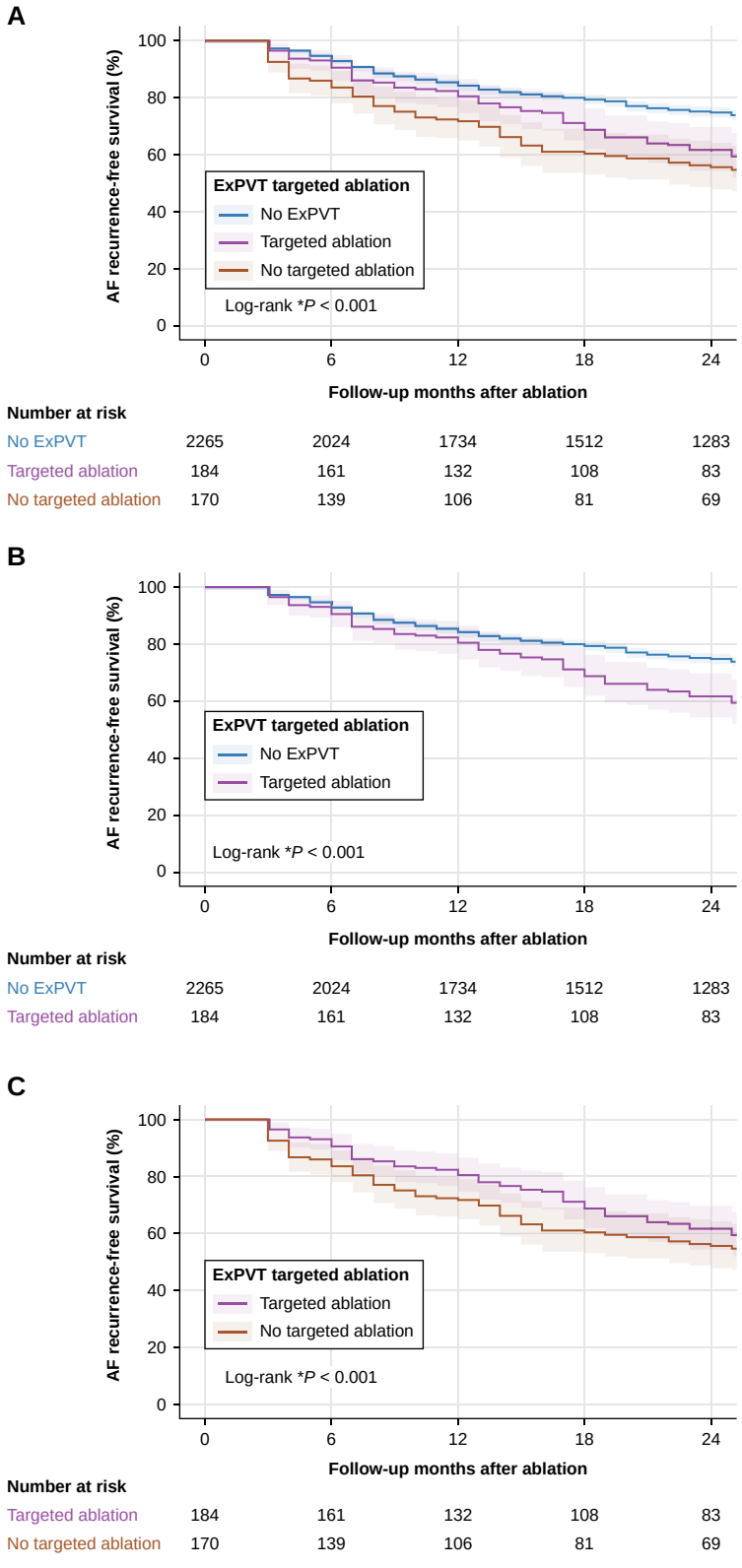


Figure 5 Kaplan–Meier survival curves for AF recurrence-free survival after RFCA according to the targeted ablation for ExPVTs. (*A*) Overall, (*B*) no ExPVT vs. ExPVT-targeted ablation, and (*C*) ExPVT-targeted ablation vs. no targeted ablation. The incidence curves and corresponding *P*-values for comparing the ExPVT-targeted ablation groups were derived from the Kaplan–Meier method with the log-rank test. The shaded area represents 95% CIs. Abbreviations: AF, atrial fibrillation; CI, confidence interval; ExPVT, extra-pulmonary vein trigger; RFCA, radio-frequency catheter ablation.

Current state and emerging issues of extra-pulmonary vein triggers

Representative mechanisms of AF recurrence after ablation include PV reconnections, autonomic neural effects, and ExPVTs.[19,22] Thus, CPVI alone may not be sufficient to control AF when non-PV foci are present.[23,24] The prevalence of ExPVTs in *de novo* RFCA is highly variable, ranging from 3.2 to 62%, depending on the provocation protocols and the precision of the mapping procedures.[25–27] In our study, ExPVTs were observed in 13.5% of the study population. Several studies have shown that ExPVTs are associated with an increased risk of AF recurrence after CPVI and that ablation of ExPVTs can reduce AF recurrence.[11,16,28,29] However, other studies suggest that targeted ablation of ExPVTs following successful CPVI may not be effective to reduce AF recurrence.[30,31] Another study reported that while targeted ablation for ExPVTs lowered the recurrence rate, patients with ExPVTs still had significantly worse rhythm outcomes compared to those without ExPVTs, even after ablation.[32] These inconsistent results may be due to an elusive mechanism, as well as limitations in mapping and ablation techniques potentially influenced by technical factors related to RFCA. Precisely mapped and targeted ExPVT ablation might be crucial in preventing avoidable AF recurrence.[11]

A comprehensive understanding of the specific characteristics of ExPVTs and defining an effective strategy for ablation targeting ExPVTs will become increasingly important.[30] Although prior guidelines lacked specific recommendations on ExPVT-targeted ablation, the 2024 EHRA/HRS/APHRS/LAHRS expert consensus has recently emphasized the role of non-PV triggers in selected patients to improve ablation outcomes.[33] Our findings align with this updated perspective, providing comprehensive data on the clinical significance of ExPVTs, and support the incorporation of systematic provocation and targeted ablation of ExPVTs into individualized AF ablation strategies.

Clinical implications of characteristics and prognostic value of extra-pulmonary vein triggers

This study highlights the clinical relevance and independent prognostic implications of ExPVTs in the context of AF recurrence after ablation. We observed significant associations between the presence of ExPVTs and several clinical and structural factors, including sex, DAT, and markers of atrial remodelling such as LA volume, wall thickness, and LA voltage. Consistent with previous studies, these variables emerged as independent predictors of ExPVTs, reinforcing their link to advanced atrial substrate pathology.[34–38] Moreover, ExPVTs were independently associated with lower mean LA voltage across both sexes. These findings align with recent studies demonstrating that baseline low-voltage areas in the LA predict AF recurrence after ablation.[39,40] Our results extend this perspective by showing that lower LA voltage is also strongly associated with the presence of ExPVTs, suggesting a shared arrhythmogenic substrate of atrial scarring and electrical remodelling.

Regarding the locations of ExPVTs, we observed that the impact on mid-term AF recurrence varied by location. Among single triggers, LA-sided and septal triggers were significantly associated with AF recurrence, whereas RA-sided triggers were not. This finding may be attributed to the relatively higher proportion of RA or SVC-septal line involvement among RA triggers, as observed in the comparison of empirical ablation strategies for RA according to the location of ExPVTs (see Supplementary material online, *Figure S6*). This pattern reflects our institutional practice of incorporating additional lesion sets, informed by prior randomized trials led by our group, and may influence the interpretation of outcomes related to ExPVT-targeted ablation.[41,42] Nevertheless, these results indicate that ExPVT location contributes to the mechanisms of AF recurrence following ablation. Previous studies have implicated LA triggers in higher AF recurrence rates, potentially due to their association with anatomic or electrical remodelling, unlike RA-sided triggers.[6] Patients with multiple or unmappable triggers had the worst rhythm outcomes. Although targeted ablation of ExPVTs improved rhythm outcomes to some extent, it did not fully offset the risk associated with these triggers. These findings suggest that the anatomical complexity and limited mappability of certain ExPVTs pose significant challenges for durable rhythm control. In this context, the results from the HRV analysis suggest that the presence of ExPVTs is associated with heightened autonomic nervous activity after RFCA. Furthermore, ExPVT-targeted ablation appears to contribute to the modulation of HRV and autonomic nervous activity, suggesting it could play a crucial role in linking targeted ablation to improved rhythm outcomes for AF recurrence. Our findings that lower mean LA wall thickness was independently predictive of favourable prognosis in mid-term AF recurrence in ExPVT patients provide a basis for further research into key variables influencing AF recurrence in this population.

Applicability and directions of extra-pulmonary vein triggers

ExPVTs are crucial factors to address for improving prognosis after AF ablation. However, detecting and eliminating ExPVTs using conventional multi-electrode catheters is challenging, as only a single ectopic beat may initiate AF, or non-PV foci may not be consistently induced, even with dedicated techniques.[11] Unsuccessful mapping and ablation of ExPVTs are associated with significantly higher AF recurrence rates.[11,43] In our study, patients with multiple or unmappable triggers and no targeted ablation for ExPVTs had the poorest rhythm outcomes. To overcome these limitations, several solutions have been proposed. A novel self-reference mapping approach using multielectrode catheters has recently shown promise in detecting ExPVTs.[44] Whole-chamber mapping, such as ECGi panoramic mapping, could offer a breakthrough, though it has limitations in localizing foci within the septum.[45] Computational modelling with an AF driver map could also guide extra-PV trigger ablation.[46]

Future directions for ExPVT-targeted treatment include identifying predisposed sites for ExPVTs using optimal mapping methods under sinus rhythm.[47] Another goal is to overcome challenges in eliminating multiple triggers. An individualized ablation strategy based on patient characteristics, referred to as a 'tailored approach,' may improve outcomes in ExPVT-targeted ablation. This requires a comprehensive understanding of ExPVTs' clinical characteristics and prognostic value. Targeted ablation of ExPVTs is a practical and effective strategy for managing patients with ExPVTs or recurrent, intractable AF.

Limitations

This study has several limitations that should be acknowledged. First, this study is a retrospective, single-centre cohort conducted over 14 years, which entails inherent limitations such as potential selection bias and limited generalizability. In addition, the lack of an internal control group without provocation test limits direct quantification of the incremental benefit of ExPVT targeting. However, our prior study showed higher recurrence rates in patients without provocation test, supporting the clinical relevance of provocation-based strategies.[32] Second, although technological advances in mapping and ablation over the long enrolment period may have introduced variability, these effects were mitigated by our consistent institutional protocols for isoproterenol provocation and uniform ablation techniques. In addition, operator experience and procedural strategies naturally evolved over time, which might have influenced outcome interpretation. Nevertheless, the prognostic significance of ExPVTs remained robust and clinically consistent, despite technological and experiential changes.

Furthermore, post-procedural AADs were selectively prescribed to patients with recurrent ExPVTs, symptomatic APBs, non-sustained AT, or early AF recurrence. Although this approach reflects real-world clinical practice, it may have influenced recurrence rates and introduced a treatment bias. Third, additional ablation strategies beyond CPVI were performed at the operator's discretion without a standardized institutional protocol, introducing variability in procedural extent and heterogeneity in outcomes that may affect the consistency and interpretation of our findings. Furthermore, the lack of a routine second isoproterenol provocation test makes it difficult to determine the success of ExPVT-targeted ablation in some cases. Fourth, LA voltage data was available for most patients (79.8%) but not all, potentially introducing selection bias and limiting the robustness of voltage-related analyses. To mitigate this limitation, multivariable models were constructed both with and without mean LA voltage. Nonetheless, incomplete voltage data remain a limitation. Fifth, the HRV analysis should be interpreted with caution, as post-RFCA HRV parameters were not available for all patients. Finally, Holter or ECG monitoring may have been insufficient to detect subclinical AF recurrence, potentially underestimating recurrence burden. However, a uniform standard follow-up schedule, complemented by clinical event surveillance and review of electronic medical records, helped minimize this limitation. A future multi-centre, prospective study with a larger patient population and standardized ablation strategies is warranted to confirm these findings and address the limitations of this study.

Conclusions

ExPVTs were strongly associated with adverse atrial substrate, reflected by lower LA voltage, and independently predicted AF recurrence after CPVI beyond established clinical factors. Location-specific effects were evident, with LA and septal triggers conferring higher recurrence risk, while multiple or unmappable triggers and lack of ExPVT-targeted ablation were consistently associated with the poorest rhythm outcomes. In conclusion, these findings highlight the prognostic significance of ExPVTs and support their systematic assessment and selective targeting in individualized AF ablation strategies.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

This work was supported by the Korea Medical Device Development Fund grant (Project number 1711174471; RS-2022-00141473) funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, and the Ministry of Food and Drug Safety) to H.-N. Pak, a grant from the Korean Cardiac Research Foundation (202303-01), and a grant from the Korean Heart Rhythm Society (KHRS2023-2) to D. Kim

Conflict of interest: None declared.

Data availability

The data used in this study can be requested in whole or in part by any qualified investigator for the purposes of replicating the analyses and results and shared by the corresponding authors upon reasonable request.

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